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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,613	04/17/2001	John Joseph Hopwood	2249/104	9830

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,613	HOPWOOD ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-31,35,36 and 60-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-31,35,36 and 60-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *12-15-03* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 19-31, 35-36, 60-66, are currently pending and under consideration in this application.

Applicants' amendments and arguments filed on 12-19-03, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The entire Office action has been rewritten. Examiner has withdrawn the rejections under 35 U.S.C. 112, 2nd paragraph and the rejections under 35 U.S.C. 112, Ist paragraph for lack of written description only. In view of the arguments presented by the applicants regarding Zhao et al. (1995) reference, Examiner has with drawn said rejection. However, all other rejections and new rejections are maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 20 recites the phrase "or other convenient means". The metes and bounds of the above phrase is not clear to the Examiner.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-28, 30-31, 35-36, 60, 62-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant enzyme having α-N-acetylglucosaminidase (NAG) activity and an amino acid sequence SEQ ID NO:2 or encoded by a nucleic acid which can hybridize under high stringency conditions to the polynucleotide sequence encoding SEQ ID NO:2, having a molecular size of 79 to 89 kDa or a pharmaceutical composition comprising such an enzyme, does not reasonably provide enablement for an NAG isolated from any or all source and having an amino acid sequence identity of 80% with that of SEQ ID NO:2 including mutants and variants and pharmaceutical compositions comprising the above enzymes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 19-28, 30-31, 35-36, 60, 62-66 are so broad as to encompass any α-N-acetylglucosaminidase isolated from any or all sources, comprising an amino acid sequence

that corresponds to a human α-N-acetylglucosaminidase or fragments or derivatives of such enzymes, including mutants and variants and pharmaceutical compositions comprising the above enzymes. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of recombinant α-N-acetylglucosaminidase broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still obtain the desired activity, requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of a single α-N-acetylglucosaminidase from a single source.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any recombinant α-N-acetylglucosaminidase because the specification does not establish: (A) regions of the protein structure which may be modified

without effecting the glucosaminidase activity; (B) the general tolerance of any or all recombinant α-N-acetylglucosaminidases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid reside of any recombinant α-N-acetylglucosaminidase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including recombinant α-N-acetylglucosaminidases from all or any sources and with an enormous number of amino acid modifications of the α-N-acetylglucosaminidase with SEQ ID NO: 2. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of α-N-acetylglucosaminidase having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants have amended claim 1 to limit the per cent homology to 80%. However, as Examiner had indicated during the interview held on 12-15-03 that he will be rejecting above claims as under non-enablement due to the 80% homology claimed for the recombinant polypeptide. Hence the above rejection is now in place.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19-31, 35-36, 60-66 rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Sasaki et al. (J. Biochem, 1991, Vol. 110:842-846). This rejection is based on the public availability of a printed publications reporting the purification of the above enzyme from various sources.

Claims 19-31, 35-36, 60-66 of the instant application are drawn to a recombinant, α-N-glucosaminidase or a fragment of the same, expressed in mammalian cells, yeast or insect cells, wherein the mammalian cell is capable of N-glycosylating the enzyme, wherein the NAG enzyme is in a glycosylated form and has a molecular weight of at least 79kDa to 89kDa when determined by SDS/PAGE and wherein the amino acid sequence of the NAG is substantially the same as that of human NAG and wherein the amino acid sequence of said enzyme is as set forth in SEQ ID NO:2 or has at least 80% sequence identity to SEQ ID NO:2 and wherein the enzyme is produced by expression of a nucleic acid which encodes the enzyme or is complementary to a

sequence encoding the enzyme and is carried in a vector capable of expression in a eukaryotic or prokaryotic cell, wherein the enzyme has an amino acid sequence that is 80% similar and encoded by a nucleic acid capable of hybridizing to SEQ ID NO:1 or 3 under high stringency conditions.

Sasaki et al. disclose the isolation and purification of the above enzyme. Sasaki et al. teach a 39,000 fold purification of a human α-N-acetylglucosaminidase (NAG) from human liver. The reference teaches that the enzyme is 80 kDa size when tested by SDS/PAGE as well as other characteristics of the enzyme. The reference also teaches that a deficiency of the above enzyme is known as MPS IIIB or Sanfilippo B syndrome a severe neurodegenerative disorder in humans. However, the reference does not teach the recombinant form of the enzyme or a pharmaceutical composition comprising the enzyme. The reference does not disclose the amino acid sequence of the enzyme or the nucleotide encoding the enzyme as capable of hybridizing to SEQ ID NO:1 or 3 under high stringency conditions. However, Examiner takes the position that the enzyme disclosed in the reference and that claimed in the instant invention are inherently one and the same. Since the enzyme has been isolated from a source identical to that in the instant application, Examiner also takes the position that the glycosylation aspect, molecular weight and the amino acid sequence the nucleotide sequence which encodes the enzyme are all inherent characteristics and that the enzyme disclosed in the reference and that claimed are one and the same. Applicants have not done anything to said enzyme except to isolate the recombinant form of the purified enzyme in the reference. Examiner sees no material, structural or functional difference between the purified and the recombinant enzyme. Therefore, Examiner takes the position that Sasaki et al. anticipates claims 19-31, 35-36, 60-66 as written based on inherency.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

Or in the alternative, Sasaki et al. render the claims 19-31, 35-36, 60-66 obvious for the following reasons. The reference not only provides a purified NAG enzyme but also clearly identifies the important role the enzyme plays in the inherited disease known as mucopolysaccharidosis IIIB. Using the purified enzyme provided in the above reference, it would have been obvious to those skilled in the art to obtain its amino acid sequence information by amino acid sequencing and isolate a cDNA clone from a cDNA library and the recombinant form of the enzyme or as a fusion protein fused to an affinity tag and expressed in any of the host cells including insect cells or CHO cells using the isolated cDNA in a vector as is well known in the art. Using such recombinant enzyme it would also have been obvious to those skilled in the art to make pharmaceutical compositions comprising the enzyme for treating the deficiency disorder. One of ordinary skill in the art would have been motivated to do so because a purified protein can be made in large amounts when obtained in the recombinant form. Furthermore, as the above reference teaches that a deficiency of the above enzyme leads to MPS IIIB disorder, it would have been obvious to those skilled in the art to provide the recombinant enzyme as a pharmaceutical composition for enzyme replacement therapy to those affected by the above disorder. One of ordinary skill in the art would have a reasonable expectation of success since

the above reference provides the purified enzyme and also teaches its role in MPS IIIB disorder and the art provides the methods to make a recombinant protein or a pharmaceutical composition comprising the same.

Therefore, Sasaki et al. render the above invention *prima facie* obvious to those skilled in the art.

In response to previous Office action, applicant has argued against the rejections of claims as anticipated by Zhao et al. claiming foreign priority date. In view of such arguments, Examiner has withdrawn those rejections and put in the place the above new rejection. Examiner has also withdrawn the previous rejection under 35 U.S.C. 103(a) as obvious in view of Sasaki et al. and rewritten the same as 35 U.S.C. 102/103 rejection.

With respect to the above rejection which was previously presented as obvious, applicant argues that the reference does not teach a recombinant form of the enzyme or a pharmaceutical composition or its use for treating MPS IIIB syndrome. Applicant also argues that the reference does not teach either nucleic acid sequence or an amino acid sequence. Applicant argues that claim 19 has been amended to recite the amino acid SEQ ID NO and as Sasaki et al. do not teach amino acid sequence information, the present invention is not obvious. Examiner respectfully disagrees with such an argument. Examiner is basing his rejection on inherency. Examiner has argued that characteristics such as amino acid sequence and other physical characteristics are inherent to the protein or the enzyme. Furthermore, applicants have not done anything except to obtain a purified protein as a recombinant protein. Applicant has not shown a material, structural or functional difference/s between the purified enzyme and the recombinant enzyme. Absent such information, the purified protein inherently possesses all the characteristics of the

recombinant enzyme even though the reference is not explicit about those characteristics. Therefore, the above rejection is maintained.

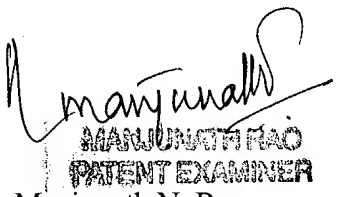
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The examiner can normally be reached on 6.30 a.m. to 3.00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao
March 30, 2004